PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10589-34-228	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/09590	International filing date *(day/month/year)* 26 March 2004 (26.03.2004)	Priority date *(day/month/year)* 27 March 2003 (27.03.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 61/00; C12Q 1/00; G01N 33/566, 573 and 574. and US CL: 435/ 4, 6, 7.2, 7.21, 41, 69.2, 91.3, 183 ; 514/ 1, 2		
Applicant PTC THERAPEUTICS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 October 2004 (26.10.2004)	16 June 2005 (16.06.2005)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Bennett Celsa Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/09590

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12.4)
- ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-150 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 151-155 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the drawings:
pages 1/2-2/2 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(e)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/09590

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 25

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 25

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/09590

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:
   - ☐ complied with.
   - ☒ not complied with for the following reasons:

See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this report has been established in respect of the following parts of the international application:
   - ☐ all parts
   - ☒ the parts relating to claims Nos. 1-24

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/09590

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 2-6, 9-10, 12, 14, 16 and 22-24	YES
	Claims 1, 7, 8, 11, 13, 15 and 17-21	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-24	NO
Industrial Applicability (IA)	Claims 1-24	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)
Please See Continuation Sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 25 is not drafted in accordance with the second and third sentences of Rule 6.4(a) and 6.4(b) since "said subject" lacks antecedent basis when referring to claim 18 and a multiple dependent claim is improperly dependent on another multiple dependent claim.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

V. 2. Citations and Explanations:
Claims 18-19 lack novelty under PCT Article 33(2) as being anticipated by US Pat. No. 5,726,195A (HILL et al.)

Hill et al. disclose small molecule antifungal (e.g anti-yeast) compounds for treating microbial infections when administered to a host (e.g. human). These compounds inhibit tRNA enzymes (e.g. synthetases) and comprise structure within the scope of the presently claimed invention (e.g. see examples and patent claims). The ability to inhibit tRNA ligase is inherently present. In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 20-21 lack novelty under PCT Article 33(2) as being anticipated by US Pat. No. 6,446,032 B1 (SCHIMMEL)

Schimmel discloses small molecule (e.g. see bottom of col. 27-28) antiproliferative (e.g chemotherapeutic agents: see col. 3) compounds for treating cancer when administered to a host (e.g. human). These RNA (e.g. tRNA) binding compounds comprise structure within the scope of the presently claimed invention (e.g. see col. 27-28, examples and patent claims). The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind tRNA. In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 18-21 lack novelty under PCT Article 33(2) as being anticipated by WO 01/25486 (RANA).

The Rana reference discloses assay-derived tRNA inhibiting (e.g. binding: see e.g. bottom of page 9-top of top of page 10; and claims, especially claims 1,2, 28-30, 40-43,) compounds within the scope of the presently claimed invention (e.g. claims 25-26) which are antiproliferative and antifungal for use in treating fungal (e.g. yeast: see i.e. claims 47-48) infections (e.g. see page 10-11 et al.) and antiproliferative disorders (e.g. cancer; i.e. see claim 46) when administered to humans. The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 18-21 lack novelty under PCT Article 33(2) as being anticipated by WO 02/083837A1(ALMSTEAD).

The Almstead reference discloses assay-derived tRNA binding compounds (e.g. see pages 3-4; bottom of page 10-11) within the scope of the presently claimed invention (e.g. see pages 21-23; claim 5) which are antiproliferative and antifungal for use in treating fungal (e.g. yeast) infections and antiproliferative disorders (e.g. cancer) when administered to humans. See claims; page 12; page 39 etc. The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any

Supplemental Box

event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 18-21 lack novelty under PCT Article 33(2) as being anticipated by WO 02/083953 A1 (RANDO et al).

The Rando et al. reference discloses assay-derived RNA binding (e.g. tRNA) compounds which effect RNA host cell factor complexes in vivo (e.g. RNA splicing; see page 10; bottom of page 12-page 13) which compounds are within the scope of the presently claimed invention (e.g. see claim 5) which are antiproliferative and antifungal for use in treating fungal (e.g. yeast) infections and antiproliferative disorders (e.g. cancer) when administered to humans. See e.g. pages 12-13; pages 47-53 et al. The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 1, 7, 8, 11, 13, 15 and 17 lack novelty under PCT Article 33(2) as being anticipated by GREER, Molecular and Cellular Biology Vol. 6, No. 2 (Feb. 1986) pages 635-644.

Greer teaches a competitive assay for joining tRNA halves (e.g. 5' and3' tRNA half molecules) in which ligation is measured between yeast ligase (e.g. a fungal tRNA splicing ligase derived from a yeast cell free extract) and T4 ligase (e.g. a "small organic" compound) as compared to a control. See e.g. Abstract; pages 638-641.

Claims 1-24 lack an inventive step under PCT Article 33(3) as being obvious over WO 01/25486 (RANA), WO 02/083937A1(ALMSTEAD) and/or WO 02/083953 A1 (RANDO et al.) in view of GREER, Molecular and Cellular Biology, HYDE-DERUYSCHER et al. Chem. & Biol. Vol. 7, No. 1 and LI et al., Science Vol. 280 (4/98).

The presently claimed invention is directed to identifying antifungal/antiproliferative compounds by screening (e.g. highthroughput) compounds (e.g. library derived) for their ability to inhibit the ligation of mammalian/yeast tRNA half molecules by inhibiting tRNA-ligase binding relative to a control.

Screening assays (e.g. highthroughput) of single compounds or compound libraries for their ability to disrupt RNA (e.g. tRNA) interactions (e.g. including splicing) in order to identify antifungal/antiproliferative drug candidates is taught by the RANA, ALMSTEAD AND/OR RANDO reference whose teaching discussed above is herby incorporated by reference in its entirety.

The RANA, ALMSTEAD AND/OR RANDO reference methods differ from the presently claimed invention by failing to explicitly teach the application of its methods to tRNA ligation assays which incorporate tRNA half molecules and tRNA ligase.

However, Li et al. teach that the tRNA splicing pathway is analogous in mammals and other organisms (e.g. fungi).

In this regard, Greer teaches a competitive assay for joining tRNA halves (e.g. 5' and3' tRNA half molecules) in which ligation is measured between yeast ligase (e.g. a fungal tRNA splicing ligase derived from a yeast cell free extract) and T4 ligase (e.g. a "small organic" compound) as compared to a control. See e.g. Abstract; pages 638-641. Greer's competitive endonuclease/ligase assays would be expected to be extrapolatable to mammalian systems in light of the Li et al. reference teaching.

Additionally, the HYDE-DERUYSCHER et al reference teaches that high-throughput screening of "small molecule" compound libraries (e.g. phage) is ideal for screening "small molecule" enzyme inhibitors for a variety of different enzymes, including ligases.

Accordingly, it would have been obvious to utilize tRNA ligation assays (e.g. incorporating tRNA half molecules and ligages) in the highthrougluput screening methods of RANA, ALMSTEAD AND/OR RANDO since these references specifically suggest screening small molecule libraries for compounds which disrupt tRNA interactions including splicing and in light of the secondary reference teaching that tRNA splicing pathway in mammals/fungi is known and analogous; and the known teaching of competitive tRNA endonuclease/ligase assays; with the desirability of using highthroughput screening of small molecular libraries for screening enzyme (e.g. ligase) binding compounds as drug candidates.

Claims 1-24 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

NONE